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Diabetes Mellitus: Can Stem Cells be the Answer?

M. Senthilnathan[1*], A. Ramadevi[2], K. Srinivas[3] and A. Thangamani[4]

[1]Department of Veterinary Pharmacology and Toxicology, NTR College of Veterinary Science, Gannavaram, Andhra Pradesh, India.
[2]Department of Animal Nutrition, Kerala Veterinary and Animal Sciences University (KVASU), Mannuthy, Kerala, India.
[3]Department of Veterinary Public Health and Epidemiology, NTR College of Veterinary Science, Gannavaram, Andhra Pradesh, India.
[4]Department of Veterinary Gynecology and Obstetrics, NTR College of Veterinary Science, Gannavaram, Andhra Pradesh, India.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MS and AR managed the literature search and wrote the first draft of the manuscript. Authors KS and AT participated in revision of this article. All authors read and approved the final manuscript.

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ABSTRACT

This review aims to enlighten the readers regarding the past, present and future of stem cells in the treatment of Diabetes. Diabetes is one of the leading causes of morbidity and mortality, affecting more than 415 million people worldwide. It is estimated that one in ten adults will have diabetes by 2030. Diabetes is mainly due to reduction in β-cell mass which are responsible for insulin production. Exogenous administration of insulin is having good impact on restoring glucose homeostasis, but it does not entirely control the minute-to-minute fluctuations in systemic blood glucose. Recently cellular-based therapies have been established for exogenous insulin administration by modern pump technology. One of the most interesting therapies involves substitution of insulin producing islet cells by transplantation. But lack of donor material and lifelong immunosuppression made the technique unfeasible. These restrictions have led to exploration of other sources of β-cells, one of the prospects being the stem cells. Several types of stem cells have

**Corresponding author: E-mail: msenthil0770@gmail.com;*

been used to make pancreatic β-cells, including human embryonic stem cells / induced pluripotent stem cells, pancreatic stem / progenitor cells, and non-pancreatic stem cells. There is also evidence of adult β-cells regeneration through β-cell replication and cellular reprogramming. Functional restoration of existing β-cells, transplantation of stem cells or stem cell-derived β-like cells might provide new opportunities for treatment. In conclusion it can be said that the research is still wide open to arrive at the efficient reprogramming of various types of stem cells to destine them towards functional β-cells.

Keywords: Diabetes Mellitus; β-cell of pancreas; stem cell therapy; pluripotent stem cells; differentiation.

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by uncontrolled high blood glucose levels. It is considered as global epidemic with continuous increase in its prevalence and incidence worldwide [1, 2]. Diabetes currently affects 8.5% of the world's population – nearly 415 million individuals worldwide. The World Health Organization predicts that diabetes deaths will double between 2015 and 2030 [3]. The statistical data on the incidence of diabetes in India is tabulated below. The major forms of the disease are Type 1 (Insulin-Dependent Diabetes Mellitus) and Type 2 diabetes (Non-Insulin Dependent Diabetes Mellitus) [4]. Pancreatic endocrine cells, especially β-cells, play a vital role in the development of both the types of diabetes. In Type 1 diabetes, the body's immune system aberrantly destroys the insulin-producing β-cells of the pancreas [5]. Type 2 diabetes is characterized both by insulin resistance, a condition in which various tissues in the body become unresponsive to insulin action, and by decline in β-cell function to the point that the cells can no longer produce enough additional insulin to overcome the insulin resistance [6].

It is possible to treat diabetes mellitus type 1 with islet transplantation [7]. Transplanted islet tissue more closely simulates the physiology of the lost islets, and patients no longer require multiple daily insulin injections. Current data revealed that 72% recipient of islets transplantation became insulin-independent [8]. However, the limited supply of immune-compatible cadaver islets/pancreas is one of the barrier that made the islet transplantation unfeasible. Deriving β-cells from stem cells presents an attractive and promising therapeutic option. Stem cells, mainly the pluripotent stem cells, demonstrate strong self-renewal abilities and have the ability to differentiate into any cell types of the body, making them a chief source for regenerative medicine and tissue engineering [9,10]. This review is intended to shed light on the prospect of use of stem cells and its types as a viable option to treat diabetes in the near future.

2. LIMITATIONS OF CONVENTIONAL DIABETES TREATMENT

Glucose homeostasis depends upon insulin secretion by pancreatic β-cells [11]. In basal conditions, insulin secreted at the rate of 2 pmol/kg/min [12] and after ingestion of meal this rate increases 5 – 10 fold [13]. Generally, human pancreas contains approximately one million islets, each containing approximately two thousand β-cells [14]. β-cells constitute 1-2 g of total pancreatic mass and 40% loss of the same can be tolerated without a significant deterioration of glucose tolerance [15]. But, further reduction in β-cell mass results in hyperglycemia. Once hyperglycemia develops 90% of β-cells have been lost [16]. Therefore, β-cell replacement is a potential therapy that might

Table 1.The Incidence of diabetes in India

1	Total adult population (20-79 years) (in 1000s)	798,988
2	Prevalence of diabetes in adults (20-79 years) (%)	8.7
3	Total cases of adults with diabetes (20-79 years) (in 1000s)	69,188.6
4	Number of deaths in adults due to diabetes (20-79 years)	1,027,911
5	Cost per person with diabetes (USD)	94.9
6	Number of cases of diabetes in adults that are undiagnosed (1000s) - yearly basis	36,061.1

Source: International Diabetes Federation (IDF), 2015

reverse the case. Pancreas transplantation is effective [17]. However, limited organ availability and the risks associated with relatively major surgery and life-long immune-suppression limits the use of this option [18]. Islet transplantation overcomes the need for major surgery but it does not overcome the limitation of organ availability and is much less successful than pancreas transplantation at accomplishing sustained insulin independence [19-21]. To overcome the shortage of available pancreas or islets for transplantation stem cells have been visualized as potential solution for the treatment of diabetes.

3. NOVEL STRATEGIES OF TREATMENT-A STEM CELLS PERSPECTIVE

Stem cells not only have the ability of self-renewal but also can give rise to differentiated cells [22,23]. Because of its proliferation and differentiation capabilities, stem cells provide a great potential for the development of novel cell-based therapies [24,25]. Type 1 diabetes might well be a suitable disease for stem cell therapy, as the causative damage is localized to a particular cell type. In theory, stem cells that can differentiate into β-cells in response to molecular signals in the local pancreatic environment could be introduced into the body, where they would migrate to the damaged tissue and differentiate as necessary to maintain the appropriate β-cell mass. As such, stem cell therapy would directly benefit persons with type 1diabetes by replenishing β-cells that are destroyed by autoimmune processes, although it would still be necessary to mitigate the autoimmune destruction of β-cells.

4. CLASSIFICATION OF STEM CELLS

According to Hongxiang Hui et al., Stem cells can be classified into 3 categories, namely:

4.1 Embryonic Stem Cells

Embryonic stem cells are pluripotent stem cells derived from the inner cell mass of the blastocyst, an early stage embryo.

4.2 Adult Stem Cells

4.2.1 Endodermal origin

Pulmonary epithelial stem cells, gastrointestinal tract stem cells, pancreatic stem cells, hepatic oval cells, mammary and prostatic gland stem cells, ovarian and testicular stem cells.

4.2.2 Mesodermal origin

Haematopoietic stem cells, mesenchymal stroma stem cells, mesenchymal stem cells, mesenchymal precursor stem cells, multipotent adult progenitor cells, bone marrow stem cells, fetal somatic stem cells, unrestricted somatic stem cells, cardiac stem cells and satellite cells of muscle.

4.2.3 Ectodermal origin

Neural stem cells, skin stem cells and ocular stem cells.

4.3 Induced Pluripotent Stem Cells

A type of pluripotent stem cells artificially derives from a non-pluripotent cell, typically an adult somatic stem cells, by inducing a “forced” expression of specific genes.

5. SOURCES OF STEM CELLS TO DERIVE PANCREATIC β-CELLS

The main sources of stem cells, includes human embryonic stem cells (hESCs)/induced pluripotent stem cells (iPSCs), pancreatic stem/progenitor cells, and non-pancreatic stem cells. There is also evidence of adult β cells regeneration through β cell replication and cellular reprogramming [26].

6. FROM HUMAN EMBRYONIC STEM CELLS TO PANCREATIC β-CELLS

Human Embryonic Stem cells (hESCs) are derived from the inner cell layer of the blastocyst [27,28] and have the ability to form cells derived from all three germ layers. These cells subsequently give rise to all differentiated cells in the adult though a series of cell fate choices that involve self-renewal and differentiation. A stepwise differentiation protocol is explored to derive functional pancreatic β cells from hESCs/iPSCs, by mimicking the signal used during embryonic pancreatic development. This involves directing ESCs first to form definitive endoderm, and then pancreatic progenitors followed by formation of endocrine progenitors, β cell precursors, and finally mature β cells.

The primary step in the protocol is to derive the definitive endoderm from hESCs with Wingless-type MMTV integration site family, member

3A (Wnt3a) and activin A treatment, expressing SOX17, a marker of definitive endoderm in ~70% cells. A chemical named Stauprimide, functions through sensitizing ESCs to a variety of differentiation signals and increase the number of endodermal cells in the presence of low levels of activin A [29]. After screening about 5000 chemicals, two compounds, named IDE-1 and IDE-2, were identified to induce the differentiation of hESCs to definitive endoderm in the absence of Wnt3a and activin A, by activating alternate pathway called TGFβ signaling pathway [30].

The next step in the protocol is differentiating definitive endoderm into pancreatic progenitors. Compound called Indolactam – V, identified to increase both number and percentage of pancreatic progenitors. The mechanism is through the activation of Protein Kinase C (PKC), although the most relevant PKC isoform has not been identified [31]. And also, Indolactam – V has been used to promote the generation of pancreatic progenitors from induced pluripotent stem cells (iPSCs) derived from type 1 Diabetes mellitus patients [32] and healthy human fibroblasts [33]. The current differentiation protocols produce a heterogeneous population, containing 50–80% *Pdx1* cells. This heterogeneous *Pdx 1* cell population is able to transform into glucose-responding cells and protects mice against streptozotocin-induced hyperglycemia in a SCID-Beige mice [34].

During embryonic pancreatic development, the pancreatic progenitors differentiate into endocrine, exocrine, and duct lineages [35]. Endocrine development is solely maintained by the key regulators namely, bHLH protein Neurogenin 3 (Ngn3), which is expressed in endocrine precursors, but reduced during differentiation [36]. Delta – Notch and TGFβ signals are critical to endocrine development [37,38]. In addition, inhibiting the Bone Morphogenetic Protein (BMP) signaling pathway by using any chemical or proteins are increasing the probability of differentiating pancreatic progenitor towards endocrine progenitor [39], which subsequently increases the efficiency to make C- peptide + cells. C – peptide or connecting peptide, is a short 31 amino acid polypeptide that connects insulin A – chain to its B – chain in the proinsulin molecule. It is the by-product of insulin biosynthesis, commonly used as a measurement of insulin gene expression [40].

The next stage is the framing of endocrine progenitors into insulin-expressing β cell precursors. Glucagon-like peptide 1 (GLP-1) receptor signaling[41], insulin signaling [42], and PI3K/AKT signaling [43] are essential for the survival and proliferation of adult β cells. Despite that, little is known about the extrinsic signal that directs the endocrine progenitor's differentiation to β cells during embryogenesis. Although different growth factors, including exendin 4 (a glucagon- like protein receptor agonist), DAPT (a g-secretase/Notch inhibitor), Hepatocyte Growth Factor (HGF), Insulin like Growth Factor-1 (IGF-1) and Fibroblast Growth Factor (FGF), or nicotinamide [44,45], are revealed during the differentiation from *Pdx1* + pancreatic progenitors to β cells, there is no strong confirmation to suggest the fruitfulness of these factors on hESC/iPSC differentiation.

The final stage in the protocol is the maturation of β cells to acquire the activity of glucose-stimulated insulin secretion (GSIS). To attain GSIS, β cell precursors need to develop the mechanism for glucose transport (such as GLUT2), glucose sensing (such as glucokinase), insulin processing, and exocytosis (such as PCSK1 and 2) [46,47]. Musculoaponeurotic fibrosarcoma oncogene homologue B and A (MafB and MafA) may partially come up with this activity during development or in response to glucose stimulation [48]. Recently, Blum et al. reported that increase in the glucose threshold results in functional β cell maturation with expression of urocortin3, a marker specifically expressed in mature β cells [49]. Currently, GSIS can be achieved only by *in vivo* implantation, and not by any *in vitro* differentiation protocol to a level similar to adult islets [50]. Therefore, the late stage β cell maturation process is still unknown and needs to be studied further.

7. FROM INDUCED PLURIPOTENT STEM CELLS TO β-CELLS

In 2006 & 2007, the Yamanaka group and the Thompson group came up with two different set of transcriptional factors such as Octamer binding transcription factor 4 (*OCT4),* Sex determining region Y box-2 *(SOX2),* Kruppel like factor 4 *(KLF4) &* Myc *(cMYC)* [51] and *OCT4, SOX2, &* Lin-28 homolog A *(LIN28)* [52] respectively, proved that adult cells can be transformed to a pluripotent stage. These cells, termed induced Pluripotent Stem Cells (iPSCs), have unlimited proliferation ability. Current studies on iPSCs revealed its applications in replacement therapy and disease modeling. The process involves delivering pluripotency

associated set of transcription factors to any adult cell types which will reprogram the cell into a pluripoptent state in which it was transdifferentiated to become β cells. Reprogramming of cells can be done across cell lineage boundaries (eg. Fibroblast to β cells) [53]. By using the stepwise differentiation protocol, human iPSCc (hiPSCs) derived from both type1 diabetes patients and healthy controls become insulin-secreting cells [54]. Using a similar stepwise protocol, Tateishi et al. showed that hiPSCs derived from the healthy skin fibroblasts can be differentiated into c-peptide expressing cells under serum-free and feeder-free conditions [55]. Another group used slightly different protocols to make glucose-responsive cells from skin fibroblast-derived iPSCs [56]. Santamaria et al. used an embryoid body-based protocol to derive c-peptide expressing cells from keratinocytes. [57]. Alipio et al. segregated iPSCs-derived insulin-secreting cells from mouse skin fibroblasts and successfully inoculated these insulin secreting cells to ameliorate hyperglycemia in types 1 and 2 diabetes mouse models [58]. Moreover, an iPSC line from rhesus monkey was observed to have an insulin-expressing nature through a stepwise process [59]. However, hESCs and iPSCs are derived using different approaches, and no systemic comparison of pancreatic differentiation potentials between hESCs and iPSCs has been performed yet.

8. CHALLENGES IN DERIVING PANCREATIC β-CELLS FROM hESCs / iPSCs

In spite current successes in directing hESCs/iPSCs into insulin-secreting cells in vitro, still many hurdles are present that needs to be overcome to use hESC-derived cells at applicaiton level. Firstly, the insulin-secreting cells derived using current stepwise protocol often express multiple endocrine hormones, such as insulin and glucagon; therefore, these cells did not resemble mature pancreatic β-cells. And also, the amount of insulin produced in hESC/iPSC-derived insulin secreting cells is much lower than adult β-cells. These insulin secreting cells do not respond to glucose stimulation in the same way as adult pancreatic β-cells [60]. Secondly, the undifferentiated cells in the hESC/hiPSC-derived heterogenous population might form teratomas after transplantation. Even though signals for differentiating hESCs/iPSCs into pancreatic cells are there, but 100% efficiency is questionable. On the other hand, teratoma forming cells may be removed from heterogeneously differentiated cells by immunodepletion with antibody against stage specific embryonic antigen-5 (SSEA-5) [61]. Thirdly, retroviral or lentiviral systems are used in differentiating iPSCs into insulin-expressing cells, which cause genetic mutation resulting in detrimental outcome. Recently, RNA delivery and protein transduction overcome those limitations by providing excisable virus free delivery of reprogramming factors [62-66], but need to be validated in cells of diabetes patients. Lastly, the microenvironment, i.e. vasculatures needed to support grafted islets cells. Vasculature niches provide an environment for insulin expression and β-cell proliferation [67,68]. Vascularization ensures not only nutrients and oxygen supply but also the intact functions of β-cells, and achieved by enhanced expression of Vascular Endothelial Growth Factor (VEGF) or co-transplant with mesenchymal stem cells (MSCs) [69-71]. On other hand, extracellular matrix components and 3-D scaffolds have been proved to facilitate the proliferation, survival, and insulin secretion of islets or purified β-cells [72,73]. To conclude, the microenvironment of grafted islets needs to be studied carefully to increase the success rate of stem cell therapy.

9. OTHER STEM CELL SOURCES TO DERIVE PANCREATIC β-CELLS

9.1 Adult Pancreatic Stem Cells

The major source for β-cell neogenesis is by the differentiation and proliferation of pancreatic duct cells using the pancreatic duct ligation model of injury [74]. Duct cells expressing carbonic anhydrase II could act as progenitors that give rise to both new islets and acinar cells after birth or after ductal ligation injury [75]. Efficient strategies need to be established to isolate and expand the adult pancreatic stem/ progenitor cells into β-cells. Pancreatic duct epithelial cells were isolated and induced *in vitro* to become function islets that responded to glucose challenge and reversed insulin - dependent diabetes [76]. Seaberg et al. reported the multiple precursor cells from adult mouse pancreas are clonally identical. Upon differentiation, individual identical colonies produced distinct populations of endocrine, exocrine cells, as well as neurons and glia. The β-like cells showed glucose-dependent responsiveness and insulin release [77]. Suzuki et al. described pancreatic stem cells, which are able to differentiate into pancreatic endocrine

and exocrine cells following transplantation using perspective isolation and clonal analysis [78]. Most of the current studies on adult pancreatic stem/progenitor cells are still at the proof of principle stage of manipulating endogenous adult pancreatic stem/progenitor cells into β-cell lineage.

9.2 Adult non-pancreatic stem cells

Adult tissue stem cells like HSCs and MSCs have the ability to transdifferentiate damage tissues and dead cells. Highly proliferative HSCs obtained from adult bone marrow undergo well-established purification methods before transplantation protocols to treat haemodynamic disorders. After autologous HSC transplantation in a patient diagnosed with type 1 diabetes mellitus, Couri et al. noticed increase in blood c-peptide levels and insulin independence [79]. Zhang et al. also showed that islet function in type 1 diabetes patients improves after HSC transplantation, but the mechanism behind that is the elimination of the islet specific autoreactive T cells but not transdifferentiation into β-cells. In addition, many recent studies reports that after transplantation, HSCs have a minor role in insulin secretion, but plays a major role in stimulating the proliferation of existing β-cells and facilitate survival of the same [80-84]. Therefore, the ability of HSCs to directly differentiate into pancreatic β-cells after transplantation is still controversial. Ianus et al. showed that the ability of bone marrow-derived cells to differentiate into pancreatic endocrine β-cells with predicted cell markers and glucose-dependent insulin secretion activity [85]. Another group also showed the ability of bone marrow-derived MSCs to transdifferentiate into insulin-secreting cells under defined conditions *in vitro* and to ameliorate hyperglycemia after transplantation [86]. Later, other groups found that after autologous transplantation, MSCs maintains a microenvironment to support existing β-cells survival and activity, produces normoglycemia [87,88]. Therefore, MSCs play supportive roles to restore hyperglycemia in diabetic animals and differentiation to pancreatic β-cells remains to be documented.

10. FROM SOMATIC CELLS TO PANCREATIC β-CELLS

10.1 Replication of β-cells

β-cells have a very low proliferating capacity, but in response to physiological changes adult β-cells gets stimulated and proliferate to maintain its mass. Nir *et al*. found replication of existing β-cells had a vital role in regeneration of pancreatic β-cells in a diabetic mouse model [89]. The β-cell mass is dynamic and balanced by β-cell formation and β-cell apoptosis. Certain physiological states like pregnancy [90], obesity and in cases of insulin resistance [91] human pancreatic β-cells can able to proliferate. Growth hormones, placental lactogen, prolactin, GLP-1, and glucose showed to stimulate β-cell population to replicate in a rodent islet model [92]. Attempts at expanding human islets *ex vivo* are being done to obtain β-cells for replacement therapy [93]. A number of structurally diverse molecule were identified that promote β-cell replication, including novel Wnt signaling agonists and L-type calcium channel agonists [94].

10.2 Reprogramming of Pancreatic Lineage

Pancreatic exocrine cells, duct cells, and other endocrine cells share development resemblance with β-cells other than somatic cells. *Ngn3, Pdx1, and MafA,* is essential for β-cell function, which reprogram mouse exocrine cells similar to β-cells *in vivo.* The induced β-cells can ameliorate hyperglycemia by reconstructing local vasculature and secreting insulin [95]. In addition, epidermal growth factor (EGF) and leukemia inhibitory factor (LIF) transdifferentiate rat exocrine cells into β-cells at low efficiency *in vitro.* After transplantation, these exocrine-derived β-cells restored normoglycemia [96]. Lineage tracing results showed that EGF signaling can transdifferentiate mouse pancreatic acinar cells into insulin-secreting cells with similar property to those of native pancreatic β-cells. Developmental transcriptional factor *NGN3* helps in reprogramming the duct cells isolated from adult human pancreas to islet β-cell genes by adenoviral [97].

Endocrine reprogramming of α-cells to β-cells can be induced by β-cell loss and exogenous gene expression. Pancreatic cell plasticity confirms large fraction of β-cells derives from glucagon producing α-cells after β-cell removal [98]. Pancreatic and duodenal homeobox 1 (*Pdx1)* could induce context-dependent α-cells reprogramming to β-cells [99].

10.3 Reprogramming from Other Adult Cells

Adult hepatocytes and pancreas share foregut endoderm, which can be successfully

reprogrammed into β-like cells. In 2000, Ferber and Karasik et al. reported that hepatocytes are able to express active insulin with *Pdx1* gene and to alleviate hyperglycemia in diabetic mice treated with streptozotocin. The protein encoded by *Pdx1* gene plays a central role in regulating pancreas development and islet cell function [100]. In 2005, the same group engineered adult human liver cells to c-peptide secreting cells in response to glucose concentration and rescue hyperglycemia in a rodent model, by introducing ectopic *Pdx1* and supplementing EGF and nicotinamide [101]. The efficiency of reprogramming can be improved by the addition of exendin-4 and *NKS6.1* genes [102,103]. Other groups used *NeuroD*and or *Ngn3* together with the *Pdx1* gene to reprogram rodent livers *in vivo* to insulin producing cells, which corrected hyperglycemia in diabetic animals [104,105]. In addition to hepatocytes, ectopic *Pdx1* expression reprograms keratinocytes to insulin-expressing cells [106].

11. CONCLUSION

The treatment of diabetes with stem cell therapy seems to have lot of scope and the ability of stem cells derived from different sources have shown promising potencies to differentiate into β cells, though the exact mechanisms of stem cell differentiation into target cells is to be unraveled. Considerable advancements have been made in the conversion of non-islet cells into islet hormone secreting cells with main aim of providing insulin secretion, and ideally glucose responsiveness, for the control of diabetes. The production of pure β cell populations from ESC, progenitor cells, or iPSCs may prove sufficient to restore glucose homeostasis. Apart from the differentiation of stem cells to islet cells *in vitro*, the major challenge in their use for diabetes is going to be the understanding of mechanisms involved in homing of differentiated cells.

12. FUTURE PROSPECT

In recent years, stem cell biology has been advancing at an extremely rapid speed and evidence is accumulating that shows the enormous potential of stem cell technology, which might hold the answer to cure some devastating disease such as diabetes. Since the iPSCs have given the option of deriving stem cells from the affected individuals without the use of embryos, the major challenge of ethical issues involved in stem cell therapy is also addressed. With respect to treatment of diabetes, unfurling the further details related to efficient stem cell differentiation to B cells without possible complications will brighten the prospect of stem cell therapy.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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